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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,669	11/08/2005	Hesson Chung	4698-0109PUS1	9231

2292 7590 08/23/2010
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EXAMINER	
PALENIK, JEFFREY T	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
08/23/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/521,669	CHUNG ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,28 and 78-91* is/are pending in the application.

4a) Of the above claim(s) *28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16 and 78-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *31 Dec 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

STATUS OF THE APPLICATION

Receipt is acknowledged of Applicants' Amendments, Remarks and Rule 132 Declaration filed, filed 9 June 2010, in the matter of Application N° 10/521,669. Said filings are entered on the record. The Examiner further acknowledges the following:

Claims 1, 5, 6, 10-13, 27, 72, 73 and 75-77 are newly cancelled.

New claims 79-91 are added. Support for the limitations is derived from the previously presented claims.

Claim 78 has been amended editorially only. Withdrawn claim 16 has been amended to depend from new claim 85. The Examiner has reconsidered the species requirement previously set forth over claim 16 and hereby rejoins the claim.

Claim 28 remains withdrawn from consideration.

No new matter has been added.

Thus, claims 16 and 78-91 now represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

One new Information Disclosure Statement (IDS), filed 31 December 2009 is acknowledged and has been considered.

WITHDRAWN OBJECTIONS/REJECTIONS

Rejections under 35 USC 112

Applicants' amendment cancelling claim 77 renders the indefiniteness rejection under 35 USC 112, second paragraph moot. Thus, said rejection has been **withdrawn**.

Rejections under 35 USC 103(a)

Applicants' amendments to the claims, as discussed above, and remarks are sufficient in overcoming the obviousness rejection made over claims 1, 5, 6, 10-13, 27, 72, 73 and 75-78 as being unpatentable over Gao et al. Applicants' Declaration having been fully considered is also persuasive in overcoming the rejection, particularly where it has been shown that diglyceride compounds would impact the novelty of the instant invention. As such, the rejection now stands **withdrawn**.

NEW REJECTIONS

In light of Applicants' newly added limitations (e.g. claims 88-90) as well as the above withdrawn rejections, the following rejection(s) are newly added:

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 78-80, 83 and 88-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller (US Pre-Grant Publication N° 2003/0059470) in further view of Woo et al. (WO 02/13815).

Claims 78-80, 83 and 88-90 are all directed to solubilized paclitaxel formulations. Claims 88-90 depend from 78-80, respectively, and further narrow the scope of the invention with the recitation of "consisting of". Claim 83 is interpreted by the Examiner as reciting the same subject matter as claims 78-80 owing to the fact that claim 83 simply recites future intended uses for the compositions of claims 78-80. Claim 91 recites that the dissolved lipophilic paclitaxel composition is further combined with (i.e., dispersed within) water.

The teachings of Muller are directed to dispersions comprising an oily phase, an aqueous phase (e.g., W/O or O/W dispersions) and at least one active ingredient which is either slightly or difficult to solubilize (claim 1). Claim 33 teaches that the oil phase comprises a mixture of lipids selected from such compounds as natural and synthetic triglycerides and monoglycerides. Paragraph [0074] teaches that lipids which are especially suited for the composition are synthetic monoglycerides and triglycerides as individual substances or mixtures thereof. Concerning the active ingredient employed in the dispersion, claim 48 expressly teaches that the active ingredient comprises at least one active such as paclitaxel. Claim 62 teaches that said active is present in the composition between 0.1-10 wt% of the dispersion.

With regard to the limitation recited in claims 79 and 89 wherein a fourth "additive" component is present ranging from 0.01-5 wt%, the Examiner considers the teachings of claims 48 and 62, discussed above as also reading on this limitation for two reasons. First the "additive" limitation is read upon by an anticancer drug. A very well known example of this is paclitaxel. That being said, any showing in the art of an amount of paclitaxel present in the dispersion ranging between 0.02-10 wt% would be considered as expressly reading on items 3) and 4) as recited in claims 79 and 89. Furthermore, the teachings of claim 48 recite other active species which also read on the "additive" limitation (e.g., cyclosporin A and taxotere).

Concerning the limitations of claims 80 and 90, a different fourth component is recited in the form of an emulsifier ranging between 0.1-90 wt% of the composition. Claims 19-22 of the Muller reference also expressly teaches that the oil-based dispersion may further

comprise an emulsifier present in an amount of at least 2 wt% (claim 22) up to at least 15 wt% (claim 20) based on the total weight of the dispersion.

Where the Muller reference is deficient is that the combinations of mono- and triglycerides which are taught do not disclose any amounts or ratios of the glycerides to one another. The monoglyceride is recited as ranging from 40-90 wt% of the composition whereas the oil component is recited as ranging from 10-60 wt%.

This deficiency is remedied by the teachings of Woo et al. which are also directed to the formulation of dosage form compositions which solubilize paclitaxel (Abstract; claims). Of particular note is that the Examples, namely Example 8, demonstrate the incorporation of paclitaxel, an emulsifier as well as a monoglyceride and/or triglyceride. In the case of Example 8, the formulation teaches glyceryl monooleate and ethyl linoleate as being present in amounts of 120 mg and 140 mg per capsule, respectively. This amounts to a monoglyceride-triglyceride ratio of about 1:1.2, a ratio which reads on the instantly claimed combination of glycerides.

Neither of the references expressly teach the range amounts of monoolein or triglyceride, as instantly claimed by Applicants. However, the values of each parameter with respect to the instantly claimed compositions are adjustable and it follows that each is a result-effective parameter that would be well within the purview of the ordinarily skilled artisan to optimize through routine experimentation (MPEP §2144.05). Both of the references teach and suggest combining monoglycerides and oils (e.g., triglycerides), but Woo teaches that the compounds may be present in a ratio which is consistent with the instantly claimed invention. Furthermore, both references expressly teach a very well-known property of paclitaxel,

namely that it is notoriously difficult to dissolve in water (i.e., that it is lipophilic). In light of this teaching, it stands to reason that the ordinarily skilled artisan would have been motivated to modify and prepare the Muller dispersion using increased amounts of both the monoolein and triglyceride compounds in combination, so as to increase or improve the likelihood of dissolving paclitaxel or controlling the degree to which the active is dispersed throughout the emulsion. The teachings of Woo et al. (e.g., Example 8) are referenced and considered relevant on the basis that they provides clear evidence in the art that: 1) combinations of monoolein and oil compounds can be used to dissolve paclitaxel (or drugs of similar solubility characteristics), and two that they can be combined in a ratio which is considered as reading on the instant claims (e.g., about a 1:1 ratio).

Based on the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonably high expectation in successfully producing the instantly claimed compositions. Therefore, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, alone or in combination, especially in the absence a clear showing of evidence to the contrary.

Claims 16, 81-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller with respect to claims 78-80 as set forth above.

Claim 34 of Muller teaches the oil component limitations of the instant claims 81 and 82, wherein the triglycerides used may embody soya oil, safflower oil long-chain triglycerides, medium-chain triglycerides, miglyols and fish oils. Medium-chain triglycerides

are further taught as preferably containing at least 90% triglycerides of caprylic acid (C_8) and of capric acid (C_{10}) (see ¶[0070]).

The limitations of claim 83 are discussed above. The reference further adds that the emulsion compositions produced by Muller can be administered using several different routes including: orally, topically and parenterally. Parenteral administration is also considered as including such routes as intracutaneous, subcutaneous, intramuscular, intra-articular and intraperitoneal ¶[0063].

The limitations of claims 85 and 16 are addressed by the reference, for example, in claims 40, 48 and 61-62. Claims 40 and 48 teach that the dispersion may contain multiple drug compounds, one of which, as discussed above, being paclitaxel. Claim 40 teaches the broader categories of those which may be included such as: anticancer drugs, antimycotics, vasoactivating agents, and immunosuppressives. Claim 48, on the other hand, teaches specific drugs such as paclitaxel, taxotere and Cyclosporin A. The teachings of claim 62 are discussed above pertaining to the metes and bounds met by a teaching of 0.2 wt% of paclitaxel. This teaching is extended with the inclusion of claim 61 which teaches that the dispersion may comprise up to about 30 wt% of the drug(s). This accounts for the possibility that the instantly claimed composition contains 10 wt% of paclitaxel and 5 wt% additive (e.g., additional drug).

The emulsifier limitations of the instant claims 86 and 87 are addressed by Muller in claims 19-22 and 24-25. Claims 19-22, as discussed above, disclose that the dispersion may contain different amounts of at least one emulsifier and/or stabilizer. Claim 24 recites that the emulsifier may be selected from such compounds as sorbitan esters, polyethylene glycol

sorbitan esters (i.e., Tween), Tween 80, and sodium lauryl (dodecyl) sulfate (SDS). Claim 25 recites embodiments for the stabilizer component which also read on the instantly claimed emulsifier. Those compounds include block-copolymers and poloxamers (e.g., Poloxamer 188 and 407).

In light of the forgoing teachings additionally provided by Muller, a person of ordinary skill in the art would have been motivated to produce the instantly claimed solubilized paclitaxel formulation. Said artisan would have similarly been motivated to produce the composition as an orally dosable emulsion or dispersion. As discussed above, the Muller reference alone provides sufficient direction so as to teach and suggest to the artisan of ordinary skill that paclitaxel may be dissolved within a lipophilic medium to form the instant composition (e.g. of instant claims 78 or 88). While the Examiner acknowledges that the Muller reference does not disclose specific examples combining a monoolein (e.g. monoglycerides) with oils (e.g. triglycerides, etc.) and paclitaxel, or with an additive (claims 79 and 89), or with an emulsifier (claims 80 and 90), it is maintained that such combinations are taught and are suggested, particularly since "[a] reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989) [see MPEP §2123(I)]. That being said, each of the different formulations (i.e., the "consisting of" *combinations of components* of claims 88-90) would have been *prima facie* obvious to a person of ordinary skill in the art, absent a clear showing of evidence to the contrary [*emphasis added*].

All claims have been rejected; no claims are allowed.

CONCLUSION

Applicants' amendments necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
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